Review article

The protective role of vagus nerve stimulation in ischemia-reperfusion injury

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A B S T R A C T

Ischemia-reperfusion injury (IRI) encompasses the damage resulting from the restoration of blood supply following tissue ischemia. This phenomenon commonly occurs in clinical scenarios such as hemorrhagic shock, severe trauma, organ transplantation, and thrombolytic therapy. Despite its prevalence, existing treatments exhibit limited efficacy against IRI. Vagus nerve stimulation (VNS) is a widely utilized technique for modulating the autonomic nervous system. Numerous studies have demonstrated that VNS significantly reduces IRI in various organs, including the heart, brain, and liver. This article reviews the pathological processes during IRI and summarizes the role and possible mechanisms of VNS in IRI of different organs. Furthermore, this review addresses the current challenges of VNS clinical applications, providing a novel perspective on IRI treatment.

1. Introduction

Ischemia-reperfusion injury (IR injury, IRI) encompasses a range of pathological processes during the restoration of blood supply following tissue ischemia. This phenomenon manifests in various clinical scenarios, such as hemorrhagic shock, severe trauma, organ transplantation, thrombolytic therapy, and so on. It can occur in the heart, brain, kidney, liver, lung, and other organs, leading to tissue damage not only in the ischemic organs but also in distant organs, with poor prognosis [1–5]. Despite its widespread occurrence, current treatments show limited efficacy in mitigating IRI. Previous studies have demonstrated that autonomic nervous system imbalance, whether excessive activation of the sympathetic nerve or inhibition of the vagus nerve, is involved in the development of IR in various organs, accelerating inflammatory reaction, oxidative stress, apoptosis, and other pathological processes [6,7].

Vagus nerve stimulation (VNS) is a prevalent method for modulating the autonomic nervous system, aiming to rebalance the autonomic nervous system by enhancing vagus nerve activity [8]. Numerous studies have demonstrated that VNS significantly reduces tissue damage and dysfunction in IRI of different organs [9,10]. This article reviews the role and potential mechanisms of VNS in IRI of various organs.

2. Pathogenesis of IRI

Despite the diverse characteristics of IRI in different organs, the fundamental pathological processes and molecular mechanisms remain the same. These intricate and interdependent processes collectively orchestrate the occurrence and development of IRI.

2.1. Oxidative/nitrification stress

Oxidative stress arises from an imbalance between reactive oxygen species (ROS) and the antioxidant system. ROS are oxygen-containing active molecules that include oxygen ions, superoxides, and oxygen-containing free radicals. Physiologically, ROS are produced as a part of oxygen metabolism and play an imperative role in maintaining homeostasis [11]. However, during the ischemic phase of IR, an excessive amount of ROS accumulates in the cells, diminishing the effectiveness of antioxidants. This can lead to secondary cell injury following the restoration of blood flow [12].

Oxidative stress can stem from both enzyme pathways and non-enzyme pathways, with the former being the main sources. The enzyme pathways include xanthine oxidase system, reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, mitochondrial electron transport chain (ETC), and uncoupling nitric oxide synthase (NOS) system. These pathways are widely involved in oxidative stress in heart, brain, liver, lung, kidney, intestine, and stomach [13]. The non-enzymatic pathway serves as a secondary source of oxidative stress, including hemoglobin and troponin, which are mainly responsible for oxidative stress in limb injury [14]. Xanthine oxidase is a pivotal enzyme in purine catabolism regulation. During ischemia, xanthine dehydrogenase is transformed into xanthine oxidase due to decreased of adenosine triphosphate (ATP) levels. Upon the restoration of blood perfusion to ischemic tissue, xanthine oxidase can convert hypoxanthine into xanthine, generating a substantial quantity of hydrogen peroxide (H_2O_2), superoxide anion, and uric acid [15] (Fig. 1). As members of the NADPH oxidase family, the Nox/Duox family can also produce a significant amount of ROS during this process, leading to the accumulation of inflammatory cells (Fig. 1). The cytokines secreted by inflammatory cells can promote the overexpression of NADPH oxidase, thereby exacerbating IRI [16]. The mitochondrial ETC complexes are crucial for ROS generation. During ischemia, complex I, II, and III are impaired and inhibited, leading to superoxide overproduction in the reperfusion phase [17]. Furthermore, the succinate accumulated in the ischemic phase is re-oxidized by succinate dehydrogenase after reperfusion, causing excessive ROS generation by reverse electron transport at complex I [18] (Fig. 4). The NOS system comprises endothelial nitric oxide synthase (endothelial NOS, eNOS), neuronal nitric oxide synthase (neuronal NOS, nNOS), and inducible nitric oxide synthase (inducible NOS, iNOS). These enzymes convert ʟ-arginine to ʟ-citrulline and produce nitric oxide (NO) [19] (Fig. 1). During ischemia, NOS has the potential to reduce oxygen to ROS, a phenomenon known as uncoupling [20] (Fig. 1). A large number of previous studies have reported that pharmacological inhibition of the mentioned oxidases can reduce ROS production during IR, thus decreasing IRI in the organ [21,22].

Nitrosative stress is primarily mediated by reactive nitrogen species (RNS). RNS are normally derived from NO and possess a heightened oxidative potential. Similar to ROS, RNS can also play a significant regulatory role in IR [23,24]. When RNS reacts with ROS, nitrogen oxides are produced, such as peroxynitrite [25]. Nitrogen oxides mediate the damage to macromolecules such as proteins, lipids, and deoxyribonucleic acids, causing necrosis of endothelial cells and parenchymal cells in the tissue. Subsequently, inflammatory cells release pro-inflammatory mediators, promoting interaction between white blood cells and endothelial cells. This process reduces the protective NO, and thus aggravating cell and tissue damage induced by IR [26].
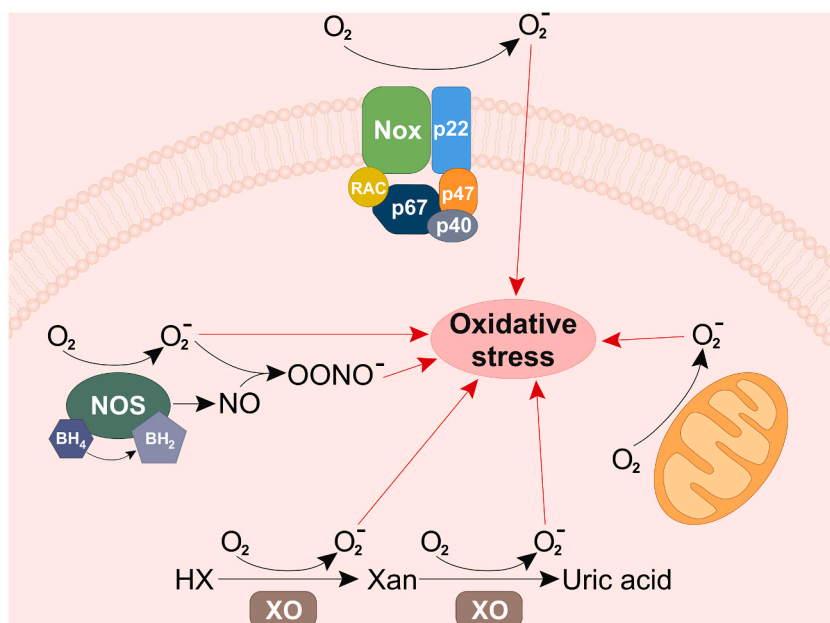

Fig. 1. The progress of oxidative/nitrification stress during IR. During ischemia, NOS can reduce oxygen to ROS and produce NO. NO reacts with superoxide ions to produce peroxynitrite ions. When ischemic tissue resumes blood perfusion, xanthine oxidase converts hypoxanthine into xanthine, and then into uric acid. This generates a large amount of hydrogen peroxide and superoxide anion. The Nox family can also produce excessive ROS during IR. Mitochondrial dysfunction caused by hypoxia can also lead to ROS overproduction. BH_2: dihydrobiopterin; BH_4: tetrahydrobiopterin; HX: hypoxanthine; NOS: nitric oxide synthase; Xan: xanthine; XO: Xanthine oxidase.

2.2. Aseptic inflammatory reaction

Due to the absence of microorganisms, the inflammatory response caused by IR is characterized as an aseptic inflammatory reaction [27]. However, it shares many similarities with the host immune response initiated by microbial invasion, marked by the production of cytokines and chemokines, as well as immune cell infiltration. During IR, damage-associated molecular patterns, such as high mobility group protein 1 (HMGB1) and ATP are released into the extracellular space or blood circulation. These molecules then bind to pattern recognition receptors, activating a series of signaling pathways, including nuclear factor kappa B (NF-κB), mitogen-activated protein kinase and type I interferon signaling pathways [28,29] (Fig. 2). NF-κB is an important transcription factor in inflammation, which further induces the expression of various pro-inflammatory cytokines [30]. Another prominent feature of the aseptic inflammatory response during IR is immune cell aggregation (Fig. 2). In the early stages of reperfusion, the main sources of infiltrating cells in injured tissue are innate immunity cells. Activated neutrophils produce ROS and release hydrolases, leading to extensive damage to parenchymal cells [31]. ROS can stimulate leukocyte adhesion and migration to endothelial cells, resulting in microvascular barrier dysfunction, no capillary reflow, and so on [31]. H_2O_2 promotes neutrophil recruitment to injured tissues [32], and inhibiting H_2O_2 production can decrease tissue damage [33]. In a renal IR model, Tanaka et al. observed that blocking H_2O_2 generation significantly reduced neutrophil infiltration and improved renal IRI [34]. Moreover, dendritic cells interact with natural killer T cells during IR and also activate the innate immune system [27]. As part of the innate immune system, the complement system assumes a crucial role. There are three ways complement is activated in IR tissue: the classical pathway, the alternative pathway, and the lectin pathway. After activation, the formation of the membrane attack complex occurs, leading to cell lysis and death [35] (Fig. 2). On the other hand, IR can trigger robust acquired immune responses, involving several cell types such as T lymphocytes. During IR, T lymphocytes gather around the infarcted tissue, in which CD4$^+$ and CD8$^+$ T lymphocytes have been found to aggravate tissue IRI [36] (Fig. 2). In addition, the production of interleukin-17 by γδT cells may contribute to the occurrence of IRI [37] (Fig. 2). In contrast to the functions of the aforementioned cells, regulatory T cells (Treg) can play a protective role in IR tissue. Increasing the number of Treg cells can significantly reduce renal IRI [38].

In addition to immune cells, platelets also play an important role in IR-related inflammation, as they can interact with various cell types to promote tissue injury [39]. Once activated during IR, platelets aggregate and adhere to endothelial cells, leukocytes, and lymphocytes, and are then transported to the injured tissue [24] (Fig. 2). Furthermore, activated platelets release pro-inflammatory cytokines, mitogenic molecules, and pro-apoptotic molecules, aggravating the inflammatory response and tissue injury [39].

In recent years, perivascular inflammation has garnered attention in the aseptic inflammatory reaction. Upon detecting damage-associated molecular patterns, fibroblasts and/or pericytes undergo a transformation into a pro-inflammatory phenotype characterized
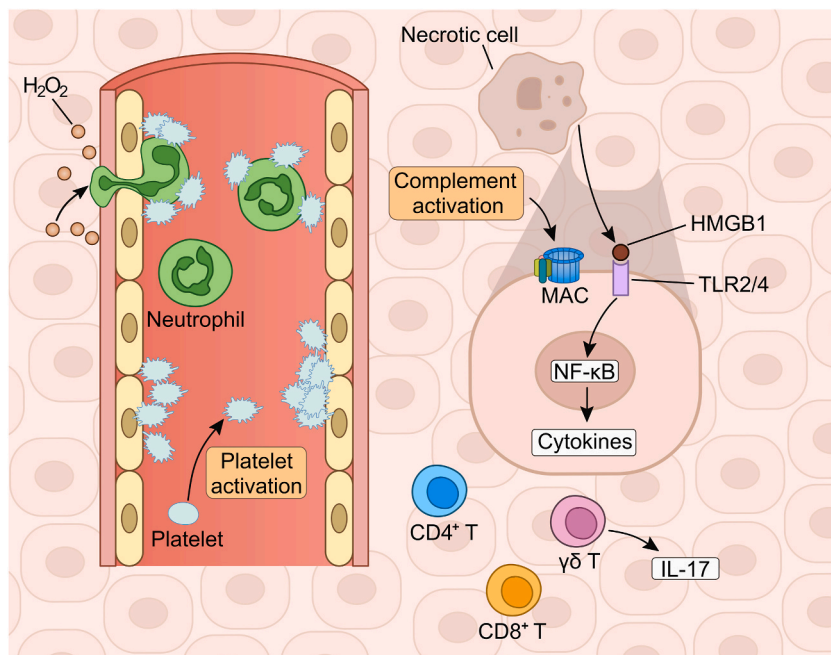

Fig. 2. The progress of aseptic inflammatory reaction during IR. During IR, damage-associated molecular patterns like HMGB1 are released by necrotic cells, which bind to pattern recognition receptors, activating the NF-κB pathway and further producing pro-inflammatory cytokines. In the initial stages of reperfusion, activated neutrophils adhere to and migrate toward endothelial cells. This leads to microvascular barrier dysfunction and no capillary reflow. H_2O_2 also promotes neutrophil recruitment to injured tissues. During IR, the complement system is activated to form the MAC, leading to cell lysis and death. Furthermore, CD4$^+$ and CD8$^+$ T lymphocytes gather around the infarcted tissue, and γδT cells also contribute to IRI by producing interleukin-17. H_2O_2: hydrogen peroxide; HMGB1: high mobility group box 1; IL-17: interleukin 17; MAC: membrane attack complex; TLR: toll-like receptor.

by the production of pro-inflammatory cytokines and chemokines, facilitating immune cell migration [40,41]. Studies have confirmed that blocking inflammatory signaling pathways in pericytes can mitigate tissue inflammation and alleviate renal IRI [42,43].

2.3. Calcium overload and mitochondrial damage

During ischemia, hypoxic cells generate ATP through glycolysis, which simultaneously results in the buildup of lactic acid, protons, and NAD^+ in the cells. This accumulation contributes to a decrease in the pH value of the cytosol [44]. To maintain an equilibrium intracellular pH, membrane Na^+/H^+ exchangers are activated, transporting H^+ ions outside the cells and Na^+ into the cells as well [44] (Fig. 3). Ischemia also leads to an insufficient supply of energy and a decrease in ATP production. Energy-dependent sodium and potassium pumps are inhibited, aggravating intracellular Na^+ accumulation [45] (Fig. 3). Consequently, Na^+/Ca^{2+} exchangers are activated, resulting in an increase in intracellular Ca^{2+} concentration [45] (Fig. 3). In the reperfusion stage, extracellular H^+ consumption increases, which further intensifies the proton concentration difference between intracellular and extracellular, accelerating intracellular calcium overload [46]. In addition, the reabsorption of Ca^{2+} by the endoplasmic reticulum/sarcoplasmic reticulum is also disturbed by IR [44] (Fig. 3).

Intracellular calcium overload can lead to cell death by initiating multiple pathways [24,47,48]. Increased intracellular calcium ions can activate calcium/calmodulin-dependent protein kinase, which is an important cause of IRI [48]. The cytoskeleton and intracellular organelles are further degraded by activated calpain, speeding up cell death [47]. Moreover, intracellular calcium overload can elevate the production of calcium pyrophosphate complex and uric acid, which bind to inflammatory body complexes, and then induce the maturation and secretion of inflammatory factors such as interleukin-1β and tumor necrosis factor-α (TNF-α). This cascade of events leads to caspase-1-dependent apoptosis [24]. In addition, excessive calcium ions in mitochondria can trigger the mitochondrial membrane permeability transition response and mitochondrial permeability transition pore (MPTP) opening [24].

MPTP opening is a pivotal event leading to cell death in pathological processes such as calcium overload and apoptosis. During IR, excessive accumulation of calcium ions, ROS, and detrimental fatty acids induces MPTP opening [22]. Hydrogen ions can be released into the cell matrix through MPTP, further inhibiting ATP synthesis [17] (Fig. 4). At the same time, water molecules in the cell matrix can enter the mitochondria through MPTP, resulting in mitochondrial swelling and rupture (Fig. 4). Under normal physiological conditions, mitochondria are dynamic organelles that participate in cytoskeleton formation, and their division and fusion are in dynamic balance. In contrast, during IR, excessive mitochondria division breaks this dynamic balance, and mitochondrial morphology cannot be maintained, which may contribute to exogenous pathway-mediated apoptosis [49]. Further, impaired mitochondrial function also reduces ATP generation and increases ROS production [50–52] (Fig. 4).
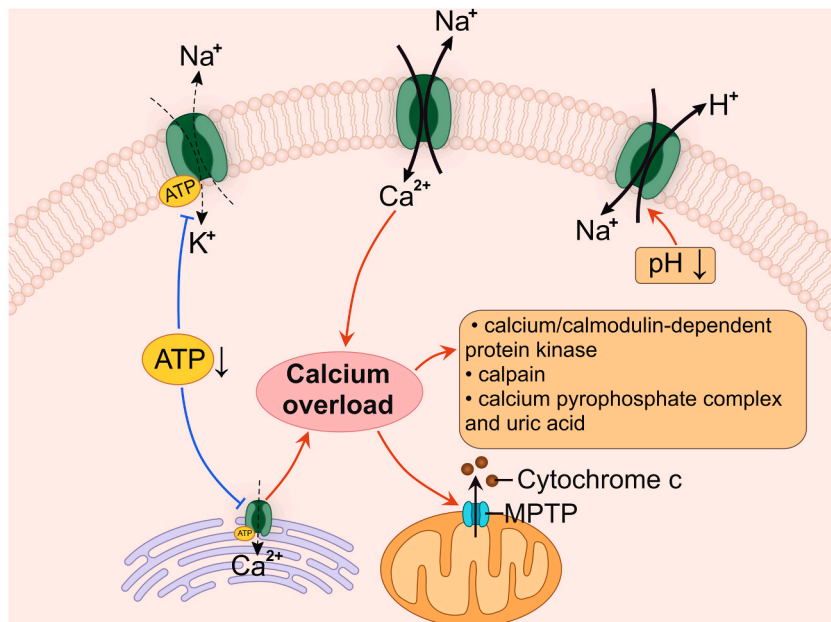

Fig. 3. The progress of calcium overload during IR. During ischemia, the cytoplasmic pH decreases. To maintain an equilibrium intracellular pH, membrane Na^+/H^+ exchangers are activated, transporting H^+ ions outside the cells and Na^+ into the cells as well. The presence of ischemia also leads to insufficient energy supply and reduced ATP production. Energy-dependent sodium and potassium pumps are inhibited, exacerbating intracellular Na^+ accumulation. Consequently, Na^+/Ca^{2+} exchangers are activated, resulting in an increase in intracellular Ca^{2+} concentration. In the reperfusion stage, extracellular H^+ consumption increases, which further exacerbates the proton concentration difference between intracellular and extracellular, accelerating intracellular calcium overload. In addition, the reabsorption of Ca^{2+} by the endoplasmic reticulum/sarcoplasmic reticulum is also disturbed. ATP: adenosine triphosphate; MPTP: mitochondrial permeability transition pore.
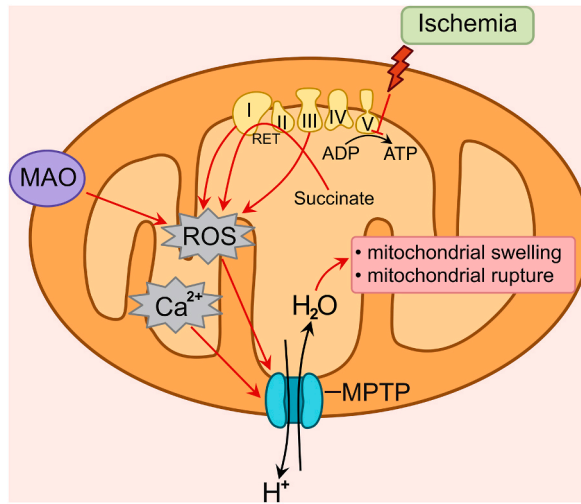
Fig. 4. The progress of mitochondrial damage during IR. During ischemia, the mitochondrial electron transport chain is inhibited due to hypoxia, so ATP production is significantly reduced. MAO located at the outer membrane of mitochondria produces large amounts of ROS. The succinate accumulated during ischemia is re-oxidized by succinate dehydrogenase after reperfusion, causing excessive ROS generation by RET at complex I. During reperfusion, the calcium content in mitochondria and ROS production increase sharply, leading to the opening of MPTP, which is the crucial link leading to cell death in pathological processes. Hydrogen ions can be released into the cell matrix through MPTP, further inhibiting ATP synthesis. At the same time, water molecules in the cell matrix can enter the mitochondria through MPTP, resulting in mitochondrial swelling and rupture. ADP: adenosine diphosphate; ATP: adenosine triphosphate; MAO: monoamine oxidase; MPTP: mitochondrial permeability transition pore; RET: reverse electron transport; ROS: reactive oxygen species.

2.4. Apoptosis

Apoptosis is a process of programmed cell death, which can be triggered by the production of ROS during IR [53]. Apoptosis involves both exogenous (death receptor signaling) and endogenous (mitochondrial) pathways. Death ligands such as TNF-α and Fas ligands bind to their respective transmembrane death receptors, forming a death signal complex. This complex activates caspase8 to
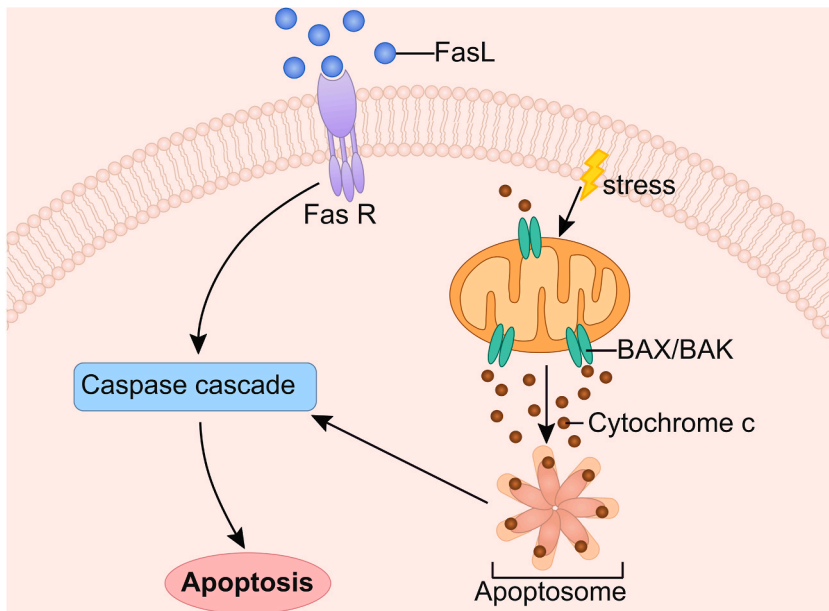

Fig. 5. The progress of apoptosis during IR. Apoptosis involves both extrinsic and intrinsic pathways. The extrinsic pathway is also known as the death receptor signaling pathway. Fas ligands combine with Fas receptors to form a death signaling complex, which activates the caspase cascade, inducing cell death by proteolysis. The intrinsic pathway, also known as the mitochondrial pathway, is activated by hypoxia and cytotoxins. Oligomerization of BAX/BAK forms a channel to release cytochrome C, which is involved in the formation of the apoptosome. FasL: Fas ligand; Fas R: Fas receptor.

cleave caspase3, inducing cell death by proteolysis [54] (Fig. 5). The endogenous pathway is activated by hypoxia and cytotoxin, which can alter the permeability of the mitochondrial membrane and activate the pro-apoptotic proteins of the B-cell lymphoma-2 (Bcl-2) family, also called apoptosis precursor proteins [55] (Fig. 5). There are three phases of apoptosis: induction, effect, and degradation. The Bcl-2 family is mainly involved in the effect phase [56], including both anti-apoptotic proteins (e.g., Bcl-2, Bcl-W, Bcl-XL, and Mcl-1) and pro-apoptotic proteins (e.g., Bad, Bax, Bcl-Xs, Bak, and Bid), which jointly regulate the process of apoptosis [57–59]. During IR, the Bad protein accumulates in the cytoplasm and then combines with Bcl-2 and Bcl-XL to process Bax and Bak, inducing the release of downstream pro-apoptotic proteins [60] (Fig. 5).

Studies have indicated that during IRI in heart, liver, kidney, and other organs, there is a noteworthy upregulation in the expression of pro-apoptotic protein Bax. Concurrently, the expression of anti-apoptotic protein Bcl-2 is significantly decreased. This shift in the balance leads to a significant increase in apoptosis in ischemic tissues [61–65]. In the renal IR model, Bcl-2 transgenic mice showed a significant decrease in activated caspase protein in the renal tubular epithelial cells and a reduction in TUNEL-positive apoptotic cells, while renal interstitial fibrosis was also markedly reduced, suggesting that Bcl-2 overexpression can relieve renal IRI [62,66,67]. Furthermore, mitigating the expression of Bax in IR tissue can also protect against IRI by inhibiting apoptosis [9].

However, with the growing recognition of alternative programmed cell death pathways like necroptosis [68], pyroptosis [69], and ferroptosis [70] in recent years, some controversy has emerged regarding the role of apoptosis in IR. Notably, in the renal IR model, inhibiting caspase8 signaling did not reduce renal tissue injury, but instead exacerbated the damage by triggering necroptosis [68]. The effects of various cell death types on IR may vary depending on ischemia duration and ischemic organ [71]. Thus, further research is imperative to identify the distinct role of these various cell death pathways.

2.5. Autophagy

Cell death induced by IR primarily involves apoptosis, necrosis and autophagy. The discussion on apoptosis has already been addressed in the preceding text. Necrosis is the most prevalent form of cell death, regarded as a passive process marked by cell disintegration, organelle swelling, and impaired mitochondrial function. Autophagy is a process in which some abnormal biological macromolecules and damaged organelles degrade in the membrane vesicles [14]. Physiologically, by removing misfolded proteins and aging damaged organelles, autophagy maintains the normal structure and function of cells. Autophagy can be induced in both ischemia and reperfusion phases [72]. In the stage of ischemia, cells can eliminate the misfolded proteins and dysfunctional mitochondria through autophagy, preventing cell death; however, in the reperfusion stage, calcium and ROS accumulate rapidly in mitochondria, and MPTP opens beyond the ability of autophagy clearance, resulting in excessive autophagy, aggravating IRI [73] (Fig. 6).

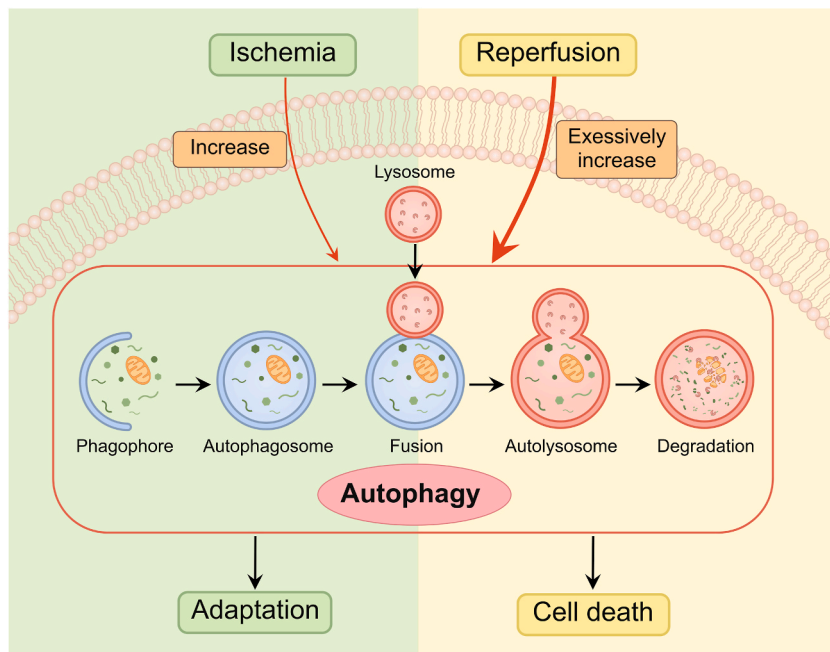**Fig. 6.** The progress of autophagy during IR. In the initial stage of ischemia, cells can eliminate the misfolded proteins and dysfunctional mitochondria through autophagy, thus inhibiting the process of cell death; however, in the reperfusion stage, the calcium and ROS in mitochondria accumulate rapidly, and MPTP opens beyond the ability of autophagy clearance, resulting in excessive autophagy, aggravating IRI.

2.6. Endoplasmic reticulum stress

The endoplasmic reticulum (ER) plays a vital role in intracellular calcium homeostasis, lipid metabolism, and protein synthesis [24]. When stressors compromise ER function, unfolded/misfolded proteins accumulate in the lumen, causing ER stress [24]. In the context of IR, ROS and pro-inflammatory cytokines activate ER stress [24,74]. ER stress triggers three distinct responses: the unfolded protein response (UPR), endoplasmic reticulum overload response, and sterol regulatory element binding protein pathway regulation, with UPR being the most pivotal [75]. UPR can improve ER stress by reducing translation activity, increasing protein folding function, and activating protein degradation [75]. Three transmembrane sensors are involved in UPR: inositol-requiring enzyme 1 (IRE1), protein kinase R-like endoplasmic reticulum kinase (PERK), and activating transcription factor 6 (ATF6) [75] (Fig. 7). Under normal circumstances, these three sensors bind to glucose-regulated protein 78 (GRP78) on the ER membrane [75]. When ER stress occurs, unfolded/misfolded proteins compete with three receptors for GRP78, thus triggering the corresponding UPR pathway to activate downstream signals, reduce protein synthesis, and enhance protein folding ability [75] (Fig. 7). Nevertheless, if ER stress persists, UPR can turn into a detrimental feedback mechanism, ultimately leading to apoptosis [75] (Fig. 7). Furthermore, ER stress contributes to IRI by promoting oxidative stress, calcium overload, inflammatory injury, and excessive autophagy [74]. Studies have shown that inhibiting ER stress-related signaling pathways, such as PERK, ATF6 and GRP78, can significantly reduce IRI [74].

3. Autonomic nervous system and IRI

3.1. Imbalance of autonomic nervous system

The autonomic nervous system consists of the sympathetic and parasympathetic nervous systems, which counteract each other to maintain a dynamic balance in a normal physiological state. Studies have indicated a substantial increase in sympathetic activity during IR in the heart, kidney, and other organs, leading to an imbalance of the autonomic nervous system [76–79]. During myocardial IR in mice, rats, and dogs, norepinephrine (NE) and epinephrine concentrations in plasma and paraventricular nucleus increased significantly, accompanied by cardiac sympathetic nerve activation [76–78]. There was also a significant rise in the incidence of malignant arrhythmias, such as ventricular extrasystole and ventricular tachycardia [76,77,80–82]. Wang et al. [78] demonstrated a change in heart rate variability (HRV) after acute myocardial infarction (AMI). As compared with the baseline level, the low frequency
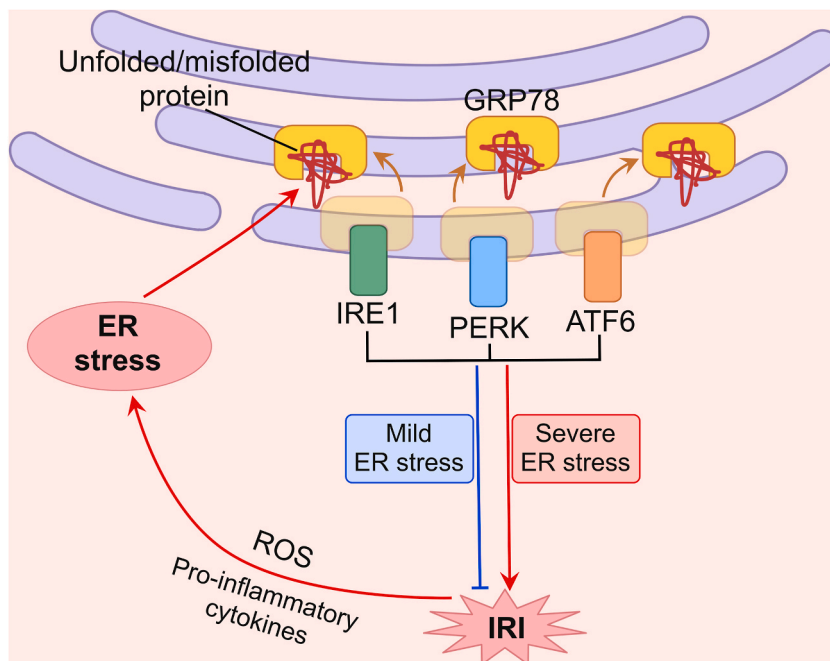

Fig. 7. The progress of ER stress during IR. ROS and pro-inflammatory cytokines activate ER stress during IR. Unfolded/misfolded proteins accumulate in the lumen.UPR can improve ER stress by reducing translation activity, increasing protein folding function, and activating protein degradation. Three transmembrane sensors are involved in UPR: IRE1, PERK, and ATF6. Under normal circumstances, these three sensors bind to GRP78) on the ER membrane. When ER stress occurs, unfolded/misfolded proteins compete with three receptors for GRP78, thus triggering the corresponding UPR pathway to activate downstream signals, reduce protein synthesis, and enhance protein folding ability. Nevertheless, when ER stress persists, UPR can become a harmful feedback mechanism that leads to apoptosis. ATF6: activating transcription factor 6; ER: endoplasmic reticulum; GRP78: glucose-regulated protein 78; IRE1: inositol-requiring enzyme 1; IRI: ischemia-reperfusion injury; PERK: protein kinase R-like endoplasmic reticulum kinase; UPR: unfolded protein response.

(LF) components increased, the high frequency (HF) components decreased, and the LF/HF ratio significantly increased, suggesting that myocardial ischemia not only activates the sympathetic nerves but also inhibits the parasympathetic nerves. Likewise, in both unilateral and bilateral renal IR models, NE concentrations in renal vein plasma and renal tissue increased significantly after reperfusion. Concurrently, renal sympathetic nerve activity rose and sustained a high level within 24 h [79,81,82]. The precise mechanisms through which IRI disrupts the balance of the autonomic nervous system are not yet fully understood. Currently, most studies believe that IRI can lead to the local accumulations of ROS, inflammatory cytokines, bradykinin, and other chemicals in ischemic tissues. These chemicals can stimulate the sensory endings of sympathetic and vagal afferent fibers, transmitting information to the central nervous system. Upon integration of this information, the central nervous system sends regulatory signals to ischemic organs, resulting in reflex inhibition of vagal activity and enhancement of sympathetic activity [83–86].

In turn, the imbalance of the autonomic nervous system may also contribute to the pathogenesis of IR, leading to worsening tissue damage. In the early stage of acute myocardial ischemia, excessive sympathetic activation is closely related to malignant cardiovascular events such as arrhythmia and sudden death [87]. Additionally, in the renal IRI model, excessive sympathetic activity can lead to the release of angiotensin II and inflammatory factors, aggravating renal damage [7]. Studies have demonstrated that the regulation of the autonomic nervous system through ablation or blockade of the sympathetic nerve can significantly improve the IRI in various organs [76,88]. It is evident that ablating or blocking of the sympathetic nerve can lead to serious complications since it disrupts the normal physiological regulatory system. The vagus nerve is a natural antagonistic system of the sympathetic nerve, so stimulating the vagus nerve can also rebalance the autonomic nervous system. The electrical VNS is a widely used in clinics, mostly to treat epilepsy and refractory depression, and its safety has been established [89]. A number of recent studies have confirmed that VNS can play a therapeutic role in IRI of various organs [90–92].

3.2. Cholinergic anti-inflammatory pathway

The interaction between the autonomic nervous system and the immune system has received growing attention over in recent decades. Borovikova et al. [93] found that electrical stimulation of the vagal efferent nerve reduced the inflammatory response to lipopolysaccharide, and vagotomy significantly enhanced the inflammatory response. Relevant studies have indicated that acetylcholine (ACh) can inhibit the release of pro-inflammatory cytokines induced by LPS. This anti-inflammatory effect disappeared after knockout of the alpha-7 nicotinic receptors (α7nAChRs) on macrophages, implying that the anti-inflammatory effect of VNS is mediated by ACh activating α7nAChRs on macrophages [94]. These results suggestthat the vagus afferent nerves can detect inflammatory signals in the surrounding tissues and transmit that information on to the brain. The efferent nerves then exert an anti-inflammatory effect and form a reflex regulation. This mechanism is referred to as the cholinergic anti-inflammatory pathway [95].

The neural mechanism of the cholinergic anti-inflammatory pathway is intricate and has not been fully elucidated. Following inflammation, cytokines and injury-related pattern molecules bind to the cytokine receptors and pattern recognition receptors expressed on the vagus afferent nerves. Once stimulated, the vagus afferent nerves convey inflammatory information to the central nucleus of the solitary tract (NTS) through nerve impulses, and then NTS transmits signals to the vagus efferent nerves [95]. On one hand, ACh released from the efferent nerve terminals binds to the α7nAChRs on macrophages, inhibiting the production of pro-inflammatory cytokines. On the other hand, the splenic nerve can be activated by the vagus efferent nerves and release NE, which binds to the β2-adrenergic receptors on choline acetyltransferase-positive T cells in the spleen. Subsequently, these T cells release ACh and interact with splenic macrophages to exert the anti-inflammatory effect [96].

Numerous studies have confirmed that cholinergic agonists or VNS can play an anti-inflammatory role in IRI by activating the cholinergic anti-inflammatory pathway [97,98]. ACh undergoes rapid degradation by acetylcholinesterase in vivo after injection. Besides, due to its non-selective agonistic nature, it can lead to adverse side effects such as vasodilation, rendering it unsuitable for use. In animal studies, nicotine has been shown to protect against IRI as a type of nAChR agonist. However, nicotine is highly addictive, so its clinical applications are severely limited [99]. Additionally, certain selective α7nAChR agonists demonstrate notable advantages in animal models due to their high specificity and few side effects [100]. However, they are typically not considered suitable for human use. VNS has been approved by the Food and Drug Administration (FDA) for treating epilepsy and refractory depression, establishing its clinical safety with a relatively certain status. Previous studies have shown that low-intensity VNS (which does not reach the heart rate change threshold) is sufficient to activate the cholinergic anti-inflammatory pathway to play a protective role [9]. Therefore, VNS may represent a viable clinical therapeutic strategy for activating the cholinergic anti-inflammatory pathway.

4. VNS plays a protective role in IRI of different organs

We searched PubMed and EMBASE for studies investigating the effects of VNS on IRI published from 1990 to 2023. The search strategy on PubMed was: ("vagus nerve"[MeSH Terms] OR ("vagus"[All Fields] AND "nerve"[All Fields]) OR "vagus nerve"[All Fields] OR "VNS"[All Fields]) AND ("ischemia reperfusion injury"[All Fields] OR ("i r"[All Fields] AND ("injurie"[All Fields] OR "injuried"[All Fields] OR "injuries"[MeSH Subheading] OR "injuries"[All Fields] OR "wounds and injuries"[MeSH Terms] OR ("wounds"[All Fields] AND "injuries"[All Fields]) OR "wounds and injuries"[All Fields] OR "injurious"[All Fields] OR "injury s"[All Fields] OR "injuryed"[All Fields] OR "injurys"[All Fields] OR "injury"[All Fields]))) AND 1990/01/01:2023/08/01[Date - Publication]. The search strategy on EMBASE was: ('vagus nerve stimulation'/exp OR 'vagus nerve stimulation' OR (('vagus'/exp OR vagus) AND ('nerve'/exp OR nerve) AND ('stimulation'/exp OR stimulation))) AND ('ischemia reperfusion injury'/exp OR 'ischemia reperfusion injury' OR (('ischemia'/exp OR ischemia) AND ('reperfusion'/exp OR reperfusion) AND ('injury'/exp OR injury))) AND [01-01-1990]/sd NOT

[01-08-2023]/sd. Using these search strategies, we retrieved 110 results on PubMed and 220 results on EMBASE. Duplicate results, conference abstracts, reviews, and non-experimental studies were excluded. As a result, 23 studies met the criteria. These studies explored the effects of VNS on IRI in the heart, brain, kidney, liver, and skeletal muscle.

4.1. Myocardial IRI

AMI is one of the leading causes of death in the world. Thrombolytic therapy, percutaneous coronary intervention, and surgical coronary artery bypass grafting can achieve reperfusion of the ischemic myocardium. This can effectively reduce infarction size, and improve cardiac function and clinical prognosis [101]. However, the reperfusion process may lead to cardiomyocyte death, resulting in serious myocardial damage, thus reducing the clinical benefits. This phenomenon is known as myocardial IRI [102]. The pathogenesis of myocardial IRI is complex, including mitochondrial damage, oxidative stress, inflammation, and apoptosis. After myocardial reperfusion, intracellular calcium overload leads to the collapse of mitochondrial membrane potential and the depletion of ATP. Consequently, ROS production increases following mitochondrial MPTP opening. The release of ROS is associated with apoptosis, DNA damage, as well as the secretion of pro-inflammatory cytokines and chemokines [103]. Unfortunately, there is currently no effective treatment for myocardial IRI [104].

Numerous studies have revealed that the autonomic nervous system plays a critical role in the development of cardiovascular diseases, and the increase in vagus nerve activity plays a cardioprotective effect [105]. Animal experimental studies have confirmed the protective effect of VNS on myocardial IRI. In the canine myocardial IR model, high-frequency electrical stimulation of the left cervical vagus nerve could inhibit oxidative stress by increasing SOD activity and reduce apoptosis by regulating the Bax/Bcl2 signaling pathway [9]. VNS significantly reduced myocardial infarction size and cardiomyocyte apoptosis index. HRV results showed that VNS reversed the overactivation of the sympathetic nerve and the decrease of vagus nerve activity induced by IR. Additionally, VNS prevented malignant ventricular arrhythmias after reperfusion. To explore whether the efferent or afferent fibers exert protective effects during VNS, Nuntaphum et al. [106] transected the middle part of the left cervical vagus nerve in pigs and gave electrical stimulation below the cross-sectional point, that is, selective VNS. The results showed that selective efferent VNS had similar protective effects as non-selective VNS. Both of them reduced myocardial infarction size, arrhythmia, oxidative stress, and apoptosis. This was done by lightning mitochondrial dysfunction, improving mitochondrial dynamics, and promoting fatty acid β oxidation. VNS modulated mitochondrial function by reducing ROS production in cardiac mitochondria and preventing mitochondrial membrane depolarization. According to these results, the myocardial protective effect of VNS is mainly realized by direct stimulation of efferent vagus nerve fibers, rather than indirect stimulation of afferent vagus nerve fibers. Another study found that left VNS at the early stage of reperfusion could significantly decrease the no-reflow range after myocardial infarction and inhibit neutrophil and macrophage infiltration into infarcted tissues [107]. This effect can be blocked by nitric oxide synthase inhibitors, suggesting that the mechanism may be related to nitric oxide signaling. Kiss et al. [108] pointed out that the protective effect of VNS on myocardial IRI can be eliminated by α7nAChR blocker or arginase. This indicates that the mechanism may be mediated by α7nAChRs. In addition, some scholars have found that VNS applied at different time points may activate different myocardial protection mechanisms. For example, pre-stimulation before ischemia can activate mAChRs and intracellular PI3K/Akt and GSK-3β expression, while VNS during reperfusion can stimulate α7nAChRs and intracellular JAK2 expression [109].

Anatomical evidence suggests that the auricular branch of the vagus nerve (ABVN) is a branch on the body surface, providing a target for non-invasive VNS. Many studies have proved that the auricular VNS exerts a similar effect to the cervical VNS. A clinical study showed that preoperative angina pectoris and arrhythmias caused by reperfusion were significantly reduced by the auricular VNS before coronary artery bypass grafting [110]. Furthermore, a single-center clinical study [111] indicated that tragus stimulation (TS) reduced myocardial IRI after PCI in patients with ST-segment elevation myocardial infarction, mainly characterized by a decrease in the occurrence of ventricular arrhythmias and a significant decline in the levels of myocardial injury markers and inflammatory cytokines within 24 h of reperfusion. Additionally, echocardiographic results showed that indexes reflecting cardiac function, such as left ventricular ejection fraction and wall motion index, were significantly improved after TS [111].

4.2. Cerebral IRI

Acute cerebral ischemia, stemming from events such as ischemic strokes, craniocerebral trauma, massive blood loss, or shock, can trigger oxidative stress, inflammatory responses, apoptosis, and cortical diffuse depolarization [112]. The most effective treatment is cerebral blood reperfusion. However, it carries the risk of secondary brain injuries such as sensory disturbance, motor disturbance, and cognitive impairment. Besides the damage caused by cerebral ischemia, cerebral IR may even compromise the patient's quality of life and long-term prognosis [113,114]. Therefore, it is necessary to seek effective measures for the prevention and treatment of cerebral IRI. Several pathophysiological cascade reactions contribute to cerebral IRI, including blood-brain barrier breakdown, energy failure, inflammation, and glutamate excitotoxicity [115]. Under hypoxia conditions, mitochondrial function is impaired and ATP synthesis becomes inadequate, resulting in ion pump dysfunction, membrane depolarization, and calcium overload. As a result of membrane depolarization, glutamate is released extracellularly and activates glutamate receptors, resulting in excitotoxicity and calcium influx [115]. Additionally, cerebral IRI activates microglia and astrocytes and increase the release of inflammatory factors [116]. ROS produced during IR can compromise the integrity of the blood-brain barrier, induce cell necrosis and enlarge the infarct area [117]. Brain neurons, microglia, and astrocytes express α7nAChRs widely in the cerebral cortex, hippocampus, and subcortex [118]. It can exert important neuroprotective effects by suppressing inflammation and promoting neuronal proliferation [118]. Previous studies have demonstrated that activation of α7nAChRs can up-regulate the expression of brain-derived neurotrophic factor (BDNF). BDNF is a

neurotrophin associated with neuroplasticity and can improve the recovery of neurological function after an ischemic stroke [119]. Therefore, VNS may play a protective role in cerebral IRI by increasing endogenous ACh production to activate α7nAChRs.

Since 1997, VNS has been approved by the FDA for treating epilepsy and refractory depression [89]. Its therapeutic potential in other nervous system diseases such as Alzheimer's disease, migraine, and cerebral infarction has attracted more and more attention [120–122]. Animal studies have confirmed the protective effect of VNS on cerebral IRI. An acute cerebral IR model in rats utilizing VNS showed a significant reduction in cerebral infarction volume. It also improved neurological function and reduced neuronal apoptosis [123]. The study found that VNS could decrease inflammatory factors and caspase-3 activation levels in the ischemic penumbra and increase p-Akt and a7nAChR levels. Therefore, VNS may activate the endogenous cholinergic pathway by up-regulating α7nAChR and p-Akt expression, thus playing an anti-inflammatory and anti-apoptotic effect on ischemic brain tissue. The team's further research suggested that the anti-inflammatory effect of VNS may be related to peroxisome proliferator-activated receptor γ (PPARγ) [124]. VNS can up-regulate PPARγ expression in the ischemic penumbra, while the neuroprotective and anti-inflammatory effects of VNS disappear in rats with PPARγ silence. Zhao et al. [125] observed that non-invasive cervical VNS can facilitate the polarization of microglia M2 by inhibiting IL-17A production. This shift in microglial polarization has an anti-inflammatory and neuroprotective role in cerebral IRI. Similarly, Zhang et al. [126] revealed that VNS can modulate microglial polarization from M1 to M2 through inhibition of TLR4/MyD88/NF-kB pathway, thereby alleviating the inflammatory response following IR. Pyroptosis, a recently identified form of programmed cell death, has been found closely related to cerebral IRI [127]. A recent study confirmed that VNS can inhibit neuronal pyroptosis in an α7nAchR-dependent way during cerebral IRI [127].

Additionally, functional studies have demonstrated that VNS can substantially improve cognitive impairments associated with cerebral IRI. Liu et al. [128] established a model of cerebral IRI by blocking the blood flow of the left middle cerebral artery in rats. They assessed the spatial memory and fear memory of rats by water maze and shuttle box behavioral tests, respectively, to gauge the functional integrity of the hippocampus and cortex. Following IRI, VNS promoted cognitive recovery, and this effect lasted for several days to weeks, indicating that acute VNS triggers the body's self-repair mechanism. After intracerebroventricular injection of neurotoxin, NE levels in cerebral cortex and hippocampus decreased significantly, and the protective effect of VNS was almost completely inhibited. These results suggest that this effect may be mediated by NE. In another study, similar results were obtained through water maze and shuttle box tests [129]. Moreover, treadmill tests showed that VNS also improved motor dysfunction caused by cerebral IRI, and its protective effects may be related to the anti-inflammatory and anti-apoptotic effects mediated by Akt and Erk2 pathways [129].

Auricular VNS plays a similar role to cervical VNS in cerebral IRI. In a rat cerebral IRI model, TS improved neurobehavioral function and axonal plasticity, increased α7nAChR and BDNF expression [130]. The protective effect was significantly weakened after blocking α7nAChRs, suggesting that α7nAChR activation may be associated with nerve function and axonal regeneration. Zhao et al. [131] revealed that TS can enhance the recovery of locomotor function after IRI by suppressing the secretion of inflammatory factors and reducing the phosphorylation of connexin 43 in the ischemic penumbra and motor cortex. In addition, TS can also promote endothelial cell proliferation and induce angiogenesis after cerebral IR [132,133]. Its molecular mechanism may be mediated by growth differentiation factor 11 and ALK5 [132,133]. Another study by the same team suggested that PPARγ may also be involved in the promotion of angiogenesis by auricular VNS in the chronic phase of ischemic stroke [134]. There is no clinical evidence that cervical VNS or auricular VNS can prevent or treat cerebral IRI, and the safety and efficacy of VNS are uncertain in patients.

4.3. Renal IRI

Acute kidney injury is characterized by a rapid decline in renal function over hours or days, resulting in electrolyte disorders and acid-base disturbances. Renal IR is a major contributor to acute kidney injury, often following shock, sepsis, and renal transplantation, increasing the risk of developing chronic and end-stage kidney diseases [135]. The clinical treatment options for renal IRI are extremely limited at present. The pathophysiological process of renal IRI involves various mechanisms, including hemodynamic changes, oxidative stress, inflammation, calcium overload, apoptosis, and necrosis [136]. When the blood supply is obstructed, renal tubular epithelial cells struggle to obtain enough oxygen and nutrients [137]. During reperfusion, the damaged tissue produces a large amount of ROS and accelerates intracellular calcium accumulation, resulting in renal tubular epithelial cell apoptosis and renal tissue injury [137]. Additionally, the production of NO is triggered by numerous activated iNOS during IR [137]. NO then reacts with superoxide anion rapidly to produce 3-NT, which directly leads to cell injury and renal dysfunction [137].

The autonomic nervous system plays a vital role in regulating renal function. Under physiological conditions, sympathetic nerves, especially renal sympathetic nerves, regulate renin secretion and renal vascular tension, and maintain water and electrolytes balance. The excessive activation of renal sympathetic nerves after renal IR, however, further exacerbates renal dysfunction and renal tissue damage [7]. Renal sympathetic denervation at the early stage of IR can reduce renal tubular injury, apoptosis, and renal fibrosis [138]. Additionally, the inhibition of sympathetic activity can play a beneficial role in renal IRI [138]. The vagus nerve-mediated cholinergic anti-inflammatory pathway is closely related to renal IRI. Yeboah et al. [139] demonstrated that nicotine or GTS-21 (a selective α7nAChR agonist) can protect against renal IRI in rats by activating the cholinergic anti-inflammatory pathway. Pretreatment with cholinergic agonist has demonstrated a significant ability to attenuate renal tubular injury and renal dysfunction. This pretreatment can also reduce tumor necrosis factor expression and inflammatory cell infiltration in renal tissue. The protective effect of nicotine is more significant than that of GTS-21, suggesting that its anti-inflammatory effect may be enhanced by activating other nAChRs. In addition, this study found that the functional nAChRs expressed on renal tubular epithelial cells may serve as a target for the cholinergic anti-inflammatory pathway. Other studies have indicated that stimulation of C1 neurons or pulsed ultrasound therapy can also alleviate renal IRI in mice by activating the cholinergic anti-inflammatory pathway [140–142]. However, α7nAChR antagonist

treatment or α7nAChR gene knockout eliminated protective effects. The above results suggest that the vagus nerve can play a protective role in renal IRI by antagonizing sympathetic activity and activating the cholinergic anti-inflammatory pathway.

The protective effects of VNS on renal IRI have been demonstrated in animal studies. Inoue et al. [143] found that left cervical VNS applied 24 h before renal ischemia can promote macrophage M2 polarization in renal tissue, thus playing an anti-inflammatory effect and alleviating renal IRI. Afferent or efferent stimulation of the vagus nerve has a similar protective effect, probably because both stimuli activate vagus preganglionic neurons. VNS had no effect on α7nAChR knockout mice, suggesting that the cholinergic anti-inflammatory pathway might be involved. In another study, VNS was applied throughout the whole IR process in a rat renal IR model [92]. Consequently, renal tubular necrosis and interstitial congestion caused by IR were reduced, and renal function was significantly improved. VNS reduced the release of inflammatory cytokines by inhibiting NF-κB pathway and played the role of antioxidant stress by decreasing the iNOS activation. Tanaka et al. [144] selectively stimulated the vagus nerve with optogenetic technique in a bilateral kidney IR model. The results showed that both efferent and afferent fibers could play a protective role. Furthermore, this study identified the C1 neurons - sympathetic nervous system - Splenic Nerve - Spleen - Kidney axis as the downstream pathway of the vagus afferent fibers. In addition to damaging the kidney itself, renal IR can also harm distant organs such as the liver, brain, and heart. The liver is more vulnerable to distant renal injury due to its rich blood supply. The mechanism may be related to systemic inflammatory response and oxidative stress. It has been reported that VNS can alleviate remote liver injury caused by acute renal IR through anti-inflammation, antioxidant stress, and anti-apoptosis [145]. However, it remains to be seen whether VNS can be applied to renal IR patients in a clinical setting.

4.4. Hepatic IRI

Hepatic IRI is a common complication during liver surgeries such as hepatectomy and liver transplantation. It can lead to graft dysfunction, liver failure, and distal organ failure, thereby increasing morbidity and mortality [146]. Hepatic IRI remains a major challenge in clinical settings, and current treatment strategies are not highly effective. The pathophysiological process of hepatic IRI can be divided into early and late stages, involving different molecular mechanisms [147]. In the early stage of reperfusion, Kupffer cells are rapidly activated by excessive complement, leading to the release of inflammatory factors and ROS, leading to liver parenchyma and vascular injury. In the late stage, increased chemokines and adhesion molecules prompt the aggregation of neutrophils in the liver parenchyma, which then release oxidants and proteases directly causing hepatocyte necrosis [148].

Sympathetic and parasympathetic fibers interact with hepatocytes to regulate crucial functions such as hepatic circulation, bile formation, and liver regeneration through various signal pathways and neurotransmitters [149]. Animal experiments have confirmed that the sympathetic nerve may promote the occurrence and development of liver injury. Oben et al. [150] observed that after chemical blockade of the sympathetic nerve with an α-1-adrenergic receptor antagonist or 6-hydroxydopamine, the number of endogenous hepatic progenitor cells in mouse liver increased and liver injury was improved. Another study concluded that sympathectomy could inhibit the hepatotoxicity of carbon tetrachloride by inhibiting liver inflammation and oxidative stress [150]. In contrast to the sympathetic nerve, the vagus nerve can exert a protective role in liver injury. Ni et al. [151] observed that hepatic vagotomy or knockout of the α7nAChR gene could promote oxidative stress induced by IR, thus aggravating liver dysfunction and hepatocyte apoptosis. In addition, many studies have indicated that activating α7nAChR through nicotine and other cholinergic receptor agonists can significantly reduce the production of inflammatory cytokines and ROS during hepatic IR, and alleviate liver injury. The underlying mechanisms may be related to the inhibition of HMGB1 expression and NF-κB activation [152,153].

Using a rat hepatic IR model, Zhang et al. [91] found that VNS reduced severe necrosis and improved liver function by inhibiting the inflammatory response, oxidative stress, and apoptosis. The molecular mechanisms may be related to the activation of Nrf2/HO-1 signaling pathways by VNS. Xia et al. [154] also reported that a 30-min VNS at 15 min after the onset of ischemia could reduce the liver tissue injury and liver dysfunction induced by IR. Furthermore, proteomic analysis revealed that plasma glutathione and glutathione peroxidase levels were significantly increased by VNS, implying that the protective effect may be related to glutathione metabolism. Furthermore, VNS can also protect distal organs against hepatic IR-induced injury, such as the lung, kidney and skeletal muscle [155–157]. Currently, there are no clinical trials examining the effect of VNS on hepatic IRI patients, and further studies are needed to confirm its effectiveness.

4.5. Skeletal muscle IRI

Skeletal muscle IRI is commonly observed in conditions such as peripheral vascular injury, osteofascial compartment syndrome, and crush syndrome. It can lead to limb and distal multi-system organ dysfunction, and may even endanger life [158]. Currently, it is widely accepted that overactivated inflammatory response and apoptosis during IR are closely related to skeletal muscle cell injury and dysfunction. Increasing evidence shows that inhibition of inflammation and apoptosis can protect skeletal muscle from IRI [159]. Dexamethasone and lipoxygen are the most commonly used drugs for skeletal muscle IRI. However, their efficacy and safety are limited, highlighting the need for continued exploration of new treatment options.

The innervation of the autonomic nervous system plays an important role in skeletal muscle. Sympathetic nerves are widely distributed in the adventitia of skeletal muscle arteries [160]. Increasing sympathetic tension increases the release of NE, which activates α-receptors, regulating vasodilator neuropeptides and vasoconstriction [161]. Ischemia and hypoxia during IR can activate sympathetic vasoconstriction and further aggravate skeletal muscle IRI [162]. Previous studies have indicated that guanidine, a sympathetic blocker, can reduce ischemic tissue injury during skeletal muscle IR [162]. Contrarily, the activation of the vagus nerve can antagonize sympathetic vasoconstriction and reduce skeletal muscle IRI. In a rat skeletal muscle IR model, Zhang et al. [90] found

for the first time that VNS significantly inhibited inflammation, oxidative stress, and apoptosis in muscle tissue, as well as serum CK and LDH levels. In addition, this study showed that VNS increased eNOS expression while decreasing ICAM-1 and VCAM-1 expression, suggesting that VNS may alleviate skeletal muscle IRI by protecting endothelial function.

5. Clinical transformation and application prospect

5.1. Current clinical application of VNS

Currently, VNS is used mostly for treating refractory epilepsy and drug-resistant depression [89]. Its efficacy and safety have been widely recognized. Since 1997, several VNS devices have been approved by the FDA for different diseases. AspireSR® and SenTiva® (Livanova, Houston, Texas, USA) are the most widely used in clinical practice and were approved by the FDA for epilepsy in 2015 and 2017 respectively [163]. Additionally, the Vivistim® system (Microtransponder, Dallas, Texas, USA) for stroke rehabilitation, the Cardiofit® VNS system (Biocontrol Medical Ltd, Yehud, Israel) for chronic heart failure, and SetPoint Medical (Santa Clarita, CA, USA)

Table 1
Studies of VNS in the treatment of IRI.

References	Species	Models	Parameters							
			Frequency (Hz)	Pulse Width (ms)	Amplitude	Side	Duration	Duty Cycle	Waveform
Chen et al., 2016 [9]	Canines	MIRI	20	0.1	The voltage of 80 % below the heart rate slowing threshold	L	2h	None	Square waves
Nuntaphum et al., 2018 [106]	Pigs	MIRI	20	0.5	3.5 mA	L	3h	21s on, 30s off	NM
Uitterdijk et al., 2015 [107]	Pigs	MIRI	25	0.3	10 mA	L	20min	None	NM
Kiss et al., 2017 [108]	Rats	MIRI	15	0.5	The voltage to reduce heart rate by 10–15 %	R	2.5h	40s on, 20s off	NM
Buchholz et al., 2018 [109]	Mice	MIRI	10	0.1	The voltage to reduce heart rate by 10–15 %	R	10min	NM	Rectangular electrical pulses
Jiang et al., 2014 [123]	Rats	CIRI	20	0.5	0.5 mA	R	1h	30s every 5min	NM
Jiang et al., 2015 [124]	Rats	CIRI	20	0.5	0.5 mA	R	1h	30s every 5min	NM
Zhang et al., 2022 [126]	Rats	CIRI	20	0.5	0.5 mA	L	1h	NM	NM
Tang et al., 2022 [127]	Rats	CIRI	20	0.5	0.5 mA	R	1h	30s on, 5min off	NM
Liu et al., 2016 [128]	Rats	CIRI	20	0.4	NM	L	20min	3s on, 3s off	NM
Jiang et al., 2015 [10]	Rats	CIRI	20	0.5	0.5 mA	R	1h	30s every 5min	NM
Xu et al., 2018 [129]	Rats	CIRI	20	0.5	0.5 mA	R	1h	30s every 5min	NM
Inoue et al., 2016 [143]	Mice	RIRI	5	1	50uA	L	10min	NM	Square waves
Wang et al., 2020 [92]	Rats	RIRI	20	0.1	The voltage to reduce heart rate by 10 %	L	6h45min	NM	NM
Tanaka et al., 2021 [144]	Mice	RIRI	5	1	50uA	L	10min	NM	Square waves
Lai et al., 2019 [145]	Rats	RIRI	20	0.1	2 mA	L	6h45min	NM	Square waves
Zhang et al., 2019 [91]	Rats	HIRI	20	0.1	The voltage to reduce heart rate by 10 %	L	7h	NM	NM
Xia et al., 2020 [154]	Rats	HIRI	10	1	50uA	L	30min	NM	Continuous single stimulation
Deng et al., 2021 [155]	Rats	HIRI	5	1	The voltage to reduce heart rate by 10 %	L	7h	1s on, 1s off	NM
Xin et al., 2021 [156]	Rats	HIRI	20	0.2	The voltage to reduce heart rate by 10 %	L	7h	NM	Square waves
Deng et al., 2022 [157]	Rats	HIRI	20	0.2	The voltage to reduce heart rate by 10 %	L	7h	NM	Square waves
Zhang et al., 2019 [90]	Rats	SMIRI	20	0.1	The voltage to reduce heart rate by 10 %	L	4.5h	NM	Square waves

CIRI: cerebral ischemia-reperfusion injury; HIRI: hepatic ischemia-reperfusion injury; IRI: ischemia-reperfusion injury; L: left; MIRI: myocardial ischemia-reperfusion injury; NM: not mentioned; R: right; RIRI: renal ischemia-reperfusion injury; SMIRI: skeletal muscle ischemia-reperfusion injury; VNS: vagus nerve stimulation.

for rheumatoid arthritis have received Investigational Device Exemption approval for clinical trials [163]. In 2015, the FDA also approved a VNS device called Maestro Rechargeable System® (EnteroMedics Inc., St Paul, MN, USA), which is implanted in the abdomen for the treatment of obesity [164]. Further, VNS may also be effective in treating migraines, Alzheimer's disease, and rheumatoid arthritis, and several clinical studies are underway [120–122].

However, VNS is an invasive nerve regulation strategy. Since nerve stimulators must be implanted surgically, surgical complications and side effects are usually inevitable [165]. Therefore, the clinical application of VNS is obviously limited. Transcutaneous cervical VNS (TcVNS) devices have attracted attention due to their noninvasive nature. GammaCore (ElectroCore LLC, Basking Ridge, NJ, USA), the most common TcVNS device, was approved by the FDA for episodic cluster headache and migraine in 2017 and 2018 respectively [163]. Nevertheless, TcVNS needs to pass through a thick skin barrier, requiring strong currents [166]. The stimulation field generated is diffuse, which can cause adverse reactions such as neck pain [166]. According to recent studies, the auricular branch of the vagus nerve is identified as a peripheral branch located on the skin surface. Its afferent fibers enter the main trunk of the vagus nerve and project to NTS [167]. As the central integration of autonomic neurons, NTS collects afferent information. It activates the caudal ventrolateral medulla and dorsal motor nucleus, and regulates autonomic central neurons. The dorsal motor nucleus transmits electrochemical signals to the epicardial ganglion plexus through the bilateral cervical vagus nerve and enhances the tension of the cardiac vagus nerve [168]. Auricular VNS is a non-invasive VNS strategy that involves the stimulation of ABVN. Similar to cervical VNS, auricular VNS can regulate cardiac autonomic dystonia characterized by sympathetic hyperfunction and parasympathetic hypofunction in heart diseases [168]. Yu et al.'s study has demonstrated that low-level TS (LL-TS) can effectively inhibit atrial fibrillation in a canine model [169]. A clinical study conducted by Po et al. [170] observed that LL-TS could inhibit atrial fibrillation and decrease inflammatory cytokines in patients with paroxysmal atrial fibrillation, suggesting that TS may be a new neuroregulatory treatment for cardiovascular diseases. In addition, Wang et al. [171] demonstrated that long-term intermittent LL-TS reduced infarct size and improved cardiac function in ischemic heart disease. The team's follow-up study [111] showed that LL-TS can reduce acute myocardial IRI in patients with acute myocardial infarction after PCI. This study introduces a novel non-invasive strategy for patients with acute myocardial infarction.

As a result, non-invasive VNS appears to be a promising alternative to traditional VNS due to its potential specificity and improved safety. However, its clinical effect needs to be further studied.

5.2. VNS parameters

In different studies, the effects of VNS exhibit some variation, which could be related to different parameters such as stimulation location, stimulation intensity, stimulation frequency, etc (Table 1). There is a close relationship between the therapeutic effects of VNS and its parameters. Optimization of VNS parameters is therefore a major problem in clinical applications.

In most studies, VNS was applied to the left cervical vagus nerve. The vagus nerve asymmetrically innervates the heart, with the left vagus nerve mainly affecting the atrioventricular node [172]. The right vagus nerve mainly affecting the sinoatrial node and atrium [172]. Therefore, stimulation of the left vagus nerve has fewer side effects on heart rate and cardiovascular function, which may be a better choice. Different intensities and frequencies of nerve stimulation also influence the effects of VNS. The cervical vagus nerve can be classified as A-, B-, and C-fibers. As A-fibers have the largest diameter, the stimulation thresholds are the lowest. Under low-intensity VNS, A-fibers are activated first, followed by B-fibers, and C-fibers are finally activated [103]. The curative effect of VNS is most closely correlated with the activations of A- and B-fibers. A stimulation frequency of 20–30Hz is a common clinical choice as it can activate both A- and B-fibers [173,174]. It has been reported that too high an intensity of VNS can cause serious adverse reactions such as a slow heart rate and respiratory rhythm changes [175]. In contrast, too low an intensity of VNS cannot activate A- and B-fibers and cannot achieve the desired therapeutic effect [175]. Additionally, different patients have different autonomic nervous system activity and pathological states, and their sensitivity to VNS varies as well. VNS stimulation intensity needs to be adjusted based on individual needs. Heart rate and heart rate variability are often used to reflect the changes in vagus nerve activity after VNS. According to clinical studies [111], VNS applied at a 50 % threshold (the minimum stimulation intensity that reduces heart rate) significantly changed heart rate variability, increased vagus nerve activity, and provided protection for patients. Clinical evidence of VNS in other organs is insufficient, and further studies are needed to confirm the optimal stimulation intensity.

6. Conclusions

Overall, IRI has a very complex pathophysiology, and the interdependence between various mechanisms complicates its treatment. Due to its ability to target multiple pathophysiological mechanisms simultaneously, VNS holds significant therapeutic potential for IRI. At present, VNS has achieved satisfactory results in preclinical and clinical studies of IRI in different organs (Fig. 8). Nevertheless, traditional cervical VNS requires neck surgery, which is traumatic and may cause postoperative complications, limiting its clinical application. In recent years, the advent of non-invasive auricular VNS has attracted wide attention, which may make up for the deficiencies of traditional cervical VNS. Previous studies have also confirmed the clinical effect of auricular VNS on myocardial IRI. Future studies should pay more attention to the safety of VNS or non-invasive VNS in IR therapy. Additionally, the optimal stimulus parameters of VNS also need to be explored.

Data availability statement

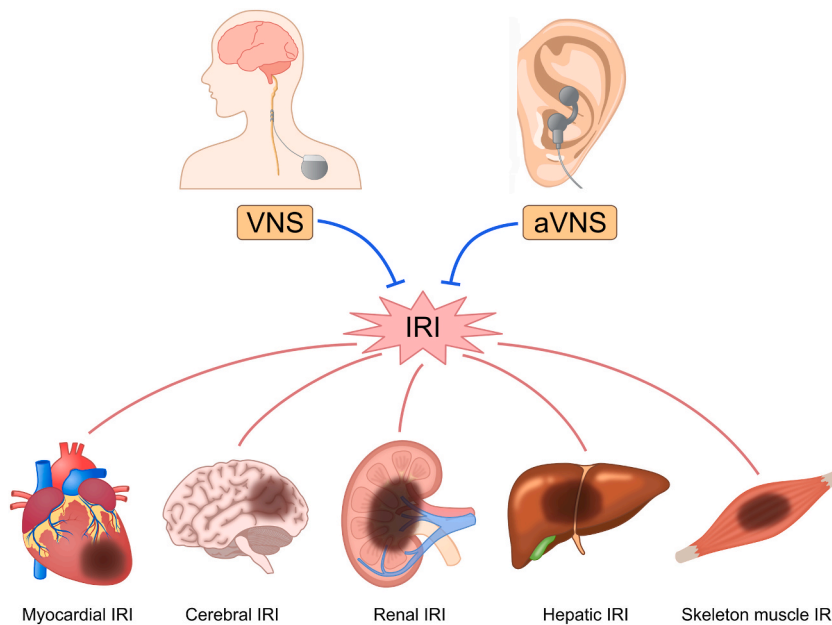No data was used for the research described in the article.

Fig. 8. VNS and aVNS attenuate IRI in various organs. IRI: ischemia-reperfusion injury; VNS: vagus nerve stimulation; aVNS: auricular vagus nerve stimulation.

CRediT authorship contribution statement

Qianqian Zhang: Writing – original draft, Funding acquisition. **Lei Zhang:** Writing – review & editing, Supervision. **Guoqiang Lin:** Writing – review & editing, Supervision. **Fanyan Luo:** Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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